Exacerbation of isoniazid induced peripheral neuropathy by pyridoxine

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Abstract

***Mycobacterium kansasii* was isolated from an area of cavitating pneumonia in a man with rheumatoid arthritis. Standard antituberculosis treatment, including isoniazid 300 mg daily, had to be stopped because of peripheral neuropathy. The patient, a slow acetylator, subjectively deteriorated despite withdrawal of isoniazid and treatment with pyridoxine 150 mg daily. Improvement occurred only after the pyridoxine had also been withdrawn. Pyridoxine may cause peripheral neuropathy and this case illustrates the need for caution in the use of this vitamin in the prevention and treatment of isoniazid induced peripheral neuropathy.**

Isoniazid has been widely used in the treatment of pulmonary tuberculosis for 35 years. Peripheral neuropathy occurs most commonly in "slow acetylators," in whom the drug's half life is prolonged,[1 2] and when higher doses are used (7·8–9·6 mg/kg daily).[3]

Pyridoxine 10 mg daily is recommended in the *British National Formulary* as prophylaxis against neuropathy, but doses of 100–200 mg daily are recommended in the treatment of established peripheral neuropathy.[1 2] In doses above 50 mg daily pyridoxine may contribute to the neuropathy.[4 5]

Case report

A 51 year old white man, a retired police officer, presented with a two month history of dry cough and weight loss. He had a six year history of seropositive rheumatoid disease, which had been controlled with fenoprofen 600 mg thrice daily and diclofenac retard 100 mg at night for the past two years, when he had been symptom free. He had never required systemic corticosteroids. Previous chest radiography had shown diffuse interstitial shadowing compatible with pulmonary fibrosis, but he admitted to no symptoms and no histopathological confirmation of this was available. Chest radiographs at admission confirmed the clinical examination findings. There was right upper lobe consolidation with cavitation, suggesting active pulmonary tuberculosis. His weight was 72 kg.

Acid-alcohol fast bacilli were seen in bronchial lavage fluid obtained at fibreoptic bronchoscopy. Standard antituberculosis chemotherapy (with rifampicin, isoniazid, and pyrazinamide) was started. Six weeks later, though improving clinically and radiographically, the patient complained of painful paraesthesiae of the extremities; a classical glove and stocking peripheral sensory deficit was evident. Pyridoxine 150 mg daily was started on the assumption that the neuropathy was due to isoniazid, and all chemotherapy was stopped. He was later confirmed to be a slow acetylator of isoniazid.

Despite these measures further deterioration occurred, with severe disabling peripheral neuritis, which was shown by electromyography to be axonal peripheral neuropathy, predominantly sensory in type and compatible with isoniazid neuropathy. Symptomatic deterioration continued until the pyridoxine was withdrawn 10 weeks later.

The acid-alcohol fast bacilli were identified in culture as *Mycobacterium kansasii*, sensitive to rifampicin and ethambutol. The patient improved clinically and radiographically with rifampicin and ethambutol treatment and a slow but appreciable improvement occurred in the peripheral neuropathy.

Discussion

Development of peripheral neuropathy is related to the state of nutrition of the patient, being much more common in poorly nourished African and Asian patients than in other groups.[3] Isoniazid induced peripheral neuropathy is associated with a deficiency of vitamin B6 (pyridoxine), an important component of protein metabolism and the synthesis of sphingomyelin.[6]

Routine haematological and biochemical assessments in our well nourished (72 kg) patient gave normal results. He was started on Rifinah 300, two tablets daily (rifampicin 600 mg and isoniazid 300 mg) and pyrazinamide 1·5 g daily. At the first sign of neuropathy the drugs were withdrawn and pyridoxine 150 mg daily was prescribed. The organism was later identified as *M kansasii* and treatment was started again, on the basis of the known sensitivities.

Deterioration in the neuropathy despite withdrawal of isoniazid and until pyridoxine was also withdrawn suggests a role for vitamin B6 in the persistence and possible exacerbation of this complication. The fact that our patient was a slow acetylator may explain the occurrence of the peripheral neuropathy but is unlikely to account for the prolonged symptoms. His rheumatoid arthritis, though clinically inactive, may also have predisposed him to peripheral neuropathy.

Large doses of vitamins were used in the 1970s to maximise the rate of the associated metabolic processes; such an approach with water soluble vitamins (B and C) was considered harmless as rapid clearance from body tissues was assumed. Schaumberg *et al*[4] described seven adults who developed severe sen-

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sory neuropathy after high dose (>2 g daily) pyridoxine. Sensory neuropathy was also reported in 23 of 58 women taking pyridoxine daily for premenstrual tension.[5] Our patient was treated with the recommended dose (150 mg daily) of pyridoxine.[1,2]

Pyridoxine is a pyridine, one of a group of chemicals known to be neurotoxic. Neurotoxicity might occur through various mechanisms. The vitamin depends on a limited and easily saturated enzyme system to cross the blood-brain barrier and is not known to be centrally neurotoxic. The cell bodies of the peripheral sensory nerves, mainly located in the dorsal ganglia, are outside the blood-brain barrier and are subject to pyridoxine toxicity.

Vitamin B6 exists in three interconvertible forms—pyridoxal phosphate, pyridoxamine, and (the least active) pyridoxine. Excess of the latter may saturate the activating enzymes pyridoxal kinase and pyridoxine phosphate oxidase, resulting in paradoxical vitamin B6 deficiency by competitive inhibition of the more active form, pyridoxal phosphate.

The dose of pyridoxine recommended by the *British National Formulary* for prophylaxis against isoniazid induced neuropathy, 10 mg daily, should not cause peripheral neuropathy and may be recommended, particularly in poorly nourished patients. Our case calls into question current recommendations[1,2] that doses in the range of 100–200 mg daily of pyridoxine should be used in patients with established peripheral neuropathy due to isoniazid.

This case has been reported to the Committee on Safety of Medicines.

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Recurrent isolated alternating phrenic nerve palsies: a variant of brachial neuritis?

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Abstract

A 40 year old man presented with three episodes of shoulder pain. This is likely to be a variant of brachial neuritis.

We report a patient who experienced three episodes of shoulder pain followed by respiratory embarrassment. Investigations on each occasion suggested an isolated phrenic nerve palsy, initially affecting the right hemidiaphragm, then the left, and subsequently the right again.

Case report

A previously healthy manual labourer first presented at the age of 26 with orthopnoea and exertional dyspnoea. This had followed a week of severe neck and shoulder pain, which resolved spontaneously. There had been no recent trauma or vaccinations. There was no relevant family history. Examination disclosed no weakness of the shoulder girdle, and no sensory deficit. A chest radiograph showed elevation of the right hemidiaphragm with paradoxical movement shown by screening. After six weeks the dyspnoea resolved and he was able to resume playing football. One year later a repeat chest radiograph was normal and screening showed the diaphragm to be moving normally.

He remained well until the age of 35, when he had a similar short lived episode of pain. After this he was again aware of difficulty in breathing when lying flat, especially after a heavy meal, and also in lifting when leaning forward. Once again there were no abnormal signs in either shoulder or arm. On this occasion radiography showed elevation and paralysis of the left hemidiaphragm with normal movement on the right. Over the next six months his symptoms improved, though he was unable to resume playing football. His chest radiograph once again returned to normal.

He presented to this unit at the age of 40 years. With no obvious precipitant he developed the same pain, which kept him awake for five nights. He found it impossible to sleep supine and on several occasions noticed early morning headache and hypersomnolence. He had discovered that he could fall asleep more easily when sitting, by rocking himself backwards and forwards. Examination showed nothing abnormal apart from inward movement of the abdomen during inspiration in the supine position.

He was investigated three months after the third episode, by which time there had been some spontaneous improvement. Routine laboratory studies gave normal results. Screening of the diaphragm showed complete paralysis on the right with paradoxical movement during deep breathing, coughing, and sneezing. Movement was normal on the left. A cervical spine radiograph showed minor degenerative changes with no encroachment on the foramina or cervical canal.

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